WARMING AND NONIRRITATING LUBRICANT COMPOSITIONS AND METHOD OF COMPARING IRRITATION.

This application is a continuation-in-part of patent application United States Serial No. 10/137,509, filed May 1, 2002, of copending patent application United States Serial No. 10/389,871, filed March 17, 2003 (Attorney Docket No. PPC 834 CIP 1), copending patent application United State Serial No. 10/390,511, filed March 17, 2003 (Attorney Docket No. PPC 834 CIP), copending patent application United States Serial No._____ (Attorney Docket No. PPC 834 CIP 3) and copending patent application United States Serial No. _____ (Attorney Docket No. PPC 834 CIP 4) which are hereby incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to clear, substantially anhydrous, gel compositions that are capable of dissolving certain azole antifungal compounds and delivering them in a soluble form. Currently, in all commercially available azole-containing antifungal and antibacterial formulations, antifungal agents such as miconazole, terconazole, itraconazole, clotrimazole and other azoles exist in insoluble form, dispersed in cream, suppository or ointment bases as micronized crystals. In general, drug agents are much more effective when delivered in a solution form. The azole compounds have almost no solubility, if any, in classical solvents used in the semisolid or solid dosage forms currently used to deliver these compounds.

BACKGROUND OF THE INVENTION

Most women, at least once in their lifetime, suffer from vaginal fungal infection. There are a variety of reasons for these infections to occur. The widespread use of antibiotics encourages the overgrowth of *Candida albicans*. This condition, known as vulvovaginitis (vulvovaginal Candidiasis or VVC) is usually treated

by azole antifungal agents applied either intravaginally or orally. However, sufferers often mistakenly believe that their vaginal infection is a fungal infection that can be treated with over-the-counter (OTC) antifungal products. Such sufferers may actually have a bacterial infection, rather than a fungal infection. OTC antifungal products are not effective against bacterial infections (also known as "bacterial vaginosis"), a chronic condition which is much more common than VVC. Clinically, bacterial vaginosis is a polymicrobial vaginal infection caused by an increase in the number of anaerobic organisms with a concomitant decrease in *Lactobacilli* in the vagina. Indiscriminate use of OTC antifungal products may lead to an added risk of masking bacterial infections.

Under stable conditions, *Lactobacilli*, the predominant organism in the normal vagina, control the growth of anaerobes and other bacteria by producing hydrogen peroxide and lactic acid from vaginal glycogen to maintain vaginal acidity. Therefore, it is of prime importance that products and compositions intended for vaginal application for treatment of fungal or bacterial infections do not adversely affect the *Lactobacilli* population and that they permit a healthy acidic vaginal pH to be maintained.

Although the incidence of vaginitis and bacterial vaginosis is staggering, there are only a small number of products currently available to treat bacterial Cleocin® (clindamycin) are available by prescription to treat bacterial vaginosis. However, it has been found that about 15-30% of patients who contract bacterial vaginosis develop a post-treatment VVC infection.

Thus, there is a pressing need for a product that will treat both VVC and bacterial vaginosis by killing the causative organisms, and thereby treat vaginal infections whether caused by fungus or bacteria.

Known treatments for VVC and bacterial vaginosis generally relate to new antifungal and antibacterial chemical entities and

penetration-enhancing formulations that increase the availability of existing compounds.

For example, WO 99/63968A1 relates to increased solubility of poorly-soluble antibacterial and antifungal agents via aqueous preparations and reversibly heat-gelling aqueous preparations using polysorbate and/or polyoxyethylene-hardened castor oil. WO99/43343A1 and US Patent No. 6,093,391 describe enhanced activity of peptide-based and other treatment agents, including azole antifungals, utilizing Pluronic P85 as a gelling agent. GB 2,327,344 discusses azole antifungal/antibacterial derivatives in formulations in combination with silver slats for treatment of wounds, ulcers and burns. GB 2,187,956 and US Patent No. 4,803,066 describe a topical pharmaceutical composition using a mixture of an antimicrobial silver compound in combination with an azole compound to treat burns, ulcers, skin and mucous membrane lesions and infections. FR 2,805,745 describes antifungal and antiseptic nail varnish compositions containing a cellulosic film forming agent in solution with an organic solvent and formalin. WO99/18791 describes the use of an amino acid derivative in the free acid or salt form, in which the nitrogen atoms of two or more amino acid molecules are linked by a hydrocarbyl substituted hydrocarbyl group as an antifungal compound and/or an antibacterial compound.

Previous efforts to solubilize azole antifungal products such as miconazole, terconazole, itraconazole, clotrimazole and others have involved the use of organic solvents such as ethyl alcohol in combination with other organic solvents. However, alcohol-based compositions are irritating to mucous membranes and cannot be used in preparations intended for vaginal or oral application.

Therefore, there remains a need for an effective, efficient product that is capable of addressing both VVC and bacterial vaginosis while selectively permitting the survival and maintenance of the vaginal *Lactobacillus* population.

One objective of this invention is to provide a means for solubilizing insoluble or sparingly-soluble azole compounds in order to increase their efficacy and spectrum of their activity. It is also an object of this invention to develop novel compositions that will be effective to treat both fungal and bacterial infections.

SUMMARY OF THE INVENTION

The compositions and methods of this invention relate to clear gel compositions in which azole compounds are incorporated in a completely soluble state. The compositions and methods of this invention contain polyols, preferably, polyhydric alcohols, as solvents for azole derivatives, more particularly, imidazoles and triazoles antifungal derivatives. The compositions of this invention also preferably contain a gelling agent, more preferably a water-soluble gelling agent, even more preferably a water-soluble cellulose gelling derivative. Preferably, the cellulose gelling derivatives useful in the compositions of this invention are hydrocolloids. Classical cellulose-based gelling agents are only water-soluble and do not form gels when used in combination with organic solvents.

There are additional advantages to the use of the compositions of this invention in delivering antimicrobial agents to patients in that the compositions of this invention may act to warm the tissue to which they are applied as well as serving to lubricate such tissue. The compositions of this invention may also be used as warming lubricant compositions that are non-toxic and non-irritating and that can be used as personal lubricants designed to come into contact with the skin or mucosa. When mixed with water, the gel and jelly compositions of this invention increase in temperature or generate warmth. This has a soothing effect on the tissues to which these compositions are applied. This substantially eliminates the feeling or perception of cold that conventional personal lubricants convey upon use.

The compositions of this invention have excellent lubrication characteristics. The gels and jelly compositions of this invention are more lubricating than even aqueous lubricant products currently available on the market. The compositions of this invention, in particular, the jelly compositions of this invention, are novel in

that their lubricity increases upon dilution with water. Known, commercially available aqueous compositions decrease in lubricity upon dilution with water. This is a particular advantage in that the compositions of this invention may be used in connection with moist vaginal or oral mucosa and will become increasingly lubricious upon exposure to the moisture therein.

Although anhydrous compositions are ordinarily perceived to be irritating to the skin and mucous membranes, the gel and jelly compositions of this invention are surprisingly non-irritating.

The compositions of this invention may be applied to the skin or mucous membranes, preferably the vaginal or oral mucosa. The compositions of this invention are preferably substantially anhydrous and preferably contain at least one polyol.

We theorize that, when the polyols contained in the compositions of this invention come into contact with water or body moisture in humans, they react with the ambient water molecules to cause an increase in temperature or generate warmth, thus having a soothing effect on the tissues to which these compositions are applied.

Surprisingly, and contrary to the general belief that polyols in compositions are irritating to the mucosa, compositions of this invention containing such polyols have been found to be non-irritating. We theorize that the hydrocolloids useful in the compositions and methods of this invention swell when they come into contact with water, yielding a lubrication coating gel. This coating physically blocks the irritant action of other anhydrous elements of the compositions of this invention. Furthermore, as the polyols useful in the compositions of this invention are humectants and moisturizers, when the hydrocolloids swell and form thin films over mucosal tissues, the films retain the moisturizers on the surface of the tissues. Thus, the compositions of this invention overcome dry conditions such as vaginal dryness and mouth dryness

caused by various factors including menopause and aging, as well as various disease conditions.

Thus, the compositions of this invention are very mild to the skin and mucous membranes. The compositions of this invention are soothing when applied to oral mucous membranes and may function to relieve minor irritation of the mouth and throat.

The combination of polyhydric alcohols in the compositions of this invention may also be used as a vehicle to solubilize otherwise insoluble drugs, including, but not limited to, antifungals, antibacterials, antivirals, analgesics, anti-inflammatory steroids, contraceptives, local anaesthetics, hormones and the like.

Preferably, the compositions of this invention are maintained at an acidic pH. An acidic pH is very helpful for the maintenance of healthy vaginal and oral flora, particularly for the maintenance of *Lactobacilli* in the vaginal area. Conventional acids or buffers are known to be insoluble in anhydrous compositions. Preferably, the compositions of this invention contain an organic acid that is soluble therein to maintain an acidic pH. Most preferably, the organic acid is lactic acid. Lactic acid is not only soluble in the anhydrous compositions of this invention, it is a natural acid generated in human tissue and is very safe for use in the compositions of this invention. Such an organic acid is particularly useful as an acidifying agent that may assist in lowering the pH of the tissues where the compositions of this invention are applied. This will help maintain the natural acidic environment of the mucosa and encourage the growth of appropriate flora.

The compositions of this invention may optionally also preferably contain an insulating agent which functions to preserve the temperature increase by maintaining the heat within the composition after it has been applied to the skin or mucosa. More preferably, honey may be utilized as an insulating agent.

This invention also relates to methods of enhancing intimacy by applying the compositions of this invention topically as a

personal lubricant or intimacy-enhancing composition. The methods of this invention may also relate to use of the compositions of this invention to mucosal surfaces, including vaginal and buccal surfaces, as a therapeutic massage medium and in other uses as set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph depicting the % viable EpiDerm cells vs Exposure Time using the composition of Example 1.

Fig. 2 is a graph depicting the % viable EpiDerm cells vs Exposure Time using the composition of Example 2.

Fig. 3 is a graph depicting the % viable EpiDerm cells vs Exposure Time using a State-of-the-Art non-irritating Product (K-Y Liquid®).

Fig. 4 is a graph depicting the % viable EpiDerm cells vs Exposure Time using a State-of-the-Art warming Product (Prosensual®)

Fig. 5 is a graph comparing the Lubricity vs Time (Seconds) of the composition of Example 1 and three leading Personal Lubricants on the market.

Fig. 6 is a graph depicting the results of a Differential Scanning Calorimetry experiment.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The compositions of this invention are substantially anhydrous, preferably containing less than about 20% water, more preferably containing less than about 5% water and, most preferably, containing less than about 3% water.

Preferably, the compositions of this invention contain at least one polyol. Preferably, the polyol is a polyhydric alcohol, and more preferably, the compositions of this invention contain at least two polyhydric alcohols. Polyethylene glycol (hereinafter,

"PEG") ethers may also be used, including PEG ethers of propylene glycol, propylene glycol stearate, propylene glycol oleate and propylene glycol cocoate and the like. Specific examples of such PEG ethers include PEG-25 propylene glycol stearate, PEG-55 propylene glycol oleate and the like. Preferably, at least one of the polyhydric alcohols of the compositions of this invention is a polyalkylene glycols or others selected from the following group: glycerine, propylene glycol, butylenes glycol, hexalene glycol or polyethylene glycol of various molecular weight and the like and/or combination thereof. More preferably, the compositions of this invention contain a polyethylene glycol; most preferably, the polyethylene glycol may be selected from the following group: polyethylene glycol 400 or polyethylene glycol 300. Polypropylene glycol of various molecular weights may also be used. PEGylated compounds such as peptide or protein derivatives obtained through PEGylation reactions may also be used. In addition, block copolymers of PEG's may be used, such as (ethylene glycol)-block-poly(propylene glycol)-block-(polyethylene glycol), poly(ethylene glycol-ran-propylene glycol) and the like. The compositions of this invention should contain polyhydric alcohols in an amount from about 80% to about 98% by weight of the composition.

The compositions of this invention should also preferably contain one or more water-soluble cellulose-derived film-forming polymers, gums, chitosans or the like. Preferably, such cellulose-derived polymers are hydroxyalkylcellulose polymers. More preferably, the hydroxyalkylcellulose polymer is selected from the following group: hydroxyethylcellulose, carboxyboxymethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose and the like. Most preferably, the hydroxyalkylcellulose polymer is hydroxypropylcellulose, such as Klucel® which is available commercially from Hercules Incorporated of Wilmington, Delaware. Most of the cellulose-derived polymers are water soluble and insoluble in anhydrous solvents but for hydroxypropylcellulose,

which is completely soluble in the anhydrous polyhydric portion of the compositions of this invention. Preferably, the compositions of this invention contain from about 0.15% to about 0.6% by weight of hydroxypropylcellulose to yield pourable gels and from about 1% to about 4% of hydroxypropylcellulose to yield thixotropic jellies.

The gel compositions of this invention most preferably contain hydroxypropylcellulose in combination with polyhydric alcohols such as propylene glycol, polyethylene glycol 300 or 400 or glycerin to completely dissolve imidazoles and triazoles antifungal compounds and form clear thixotropic gels.

Solubilizing these compounds not only increases their efficacy, it also increases the spectrum of their activity. Surprisingly, these antifungal compounds in soluble form have been found to exert antibacterial activity in addition to their antifungal activity. The treatment agents in an insoluble state cannot readily and directly permeate fungal or bacterial cell walls, thus limiting their availability and restricting their mode of action. Once the compounds are rendered soluble, they are able to permeate into the fungal and bacterial cell walls. Because this increases their effectiveness against organisms, a much lower concentration or dose of compound is required to treat an infection. Furthermore, they are now able to treat infections caused by more than one type of organism simultaneously. This will make the treatment of vaginal infections simpler and more practical, as women will be able to use one preparation to treat infections whatever the causative organism.

Another surprising advantage of the compositions of this invention is that the presence of lactic acid in the compositions of this invention serves to maintain a healthy acidic vaginal pH and, therefore, a healthy *Lactobacillus* population. The compositions of this invention are surprisingly selective in that that combat fungal and unwanted bacterial cells while maintaining the appropriate vaginal flora population. The compositions of this invention may

optionally and preferably also contain an insulating agent. More preferably, the insulating agent should be honey or esters of isopropyl alcohol and saturated high molecular weight fatty acids such as myristic or palmitic acid, e.g., isopropyl myristate and isopropyl palmitate . The insulating agent should be present in the compositions of this invention in an amount of from about 1% to about 5% by weight of the composition. However, other filler-type agents may be utilized that can assist in retaining heat, such as materials with high bulk properties or materials that raise resistance to heat loss, known to those of skill in the art. Such materials may include aluminosilicates (for example, clay, zeolites and the like), alkyl celluloses and other cellulose derivatives and other like materials know to those of skill in the art.

Surprisingly, the compositions of this invention actually increase in temperature upon exposure to moisture from the skin or mucosa, without causing undue irritation or harm to the skin or mucosal surfaces. This distinguishes them from previously-known products that merely conveyed the sensation of warming by causing irritation to the topical surface to which they were applied.

This warming characteristic is brought about by the exothermic release of energy generated upon exposing the compositions of this invention to water. As set forth below in Example 6, the amount of energy released by the compositions of this invention, and in turn the potential temperature increases, upon exposure to water may be calculated or measured in accordance with the procedures set forth therein. Preferably, the temperature increase of the compositions of this invention range from the minimum perceptible temperature increase to no more than would be perceived as a "burning" sensation to the skin or mucosa, thus causing irritation or insult to the skin or mucosa. Such a temperature might be about 40°F or more.

Preferably, the amount of energy released (hereinafter, "Energy Release Index") by solubilizing the compositions of this invention is from about 11 to about 40mJ/mg (milliJoules per

milligram). The associated preferred temperature rise range is at least about 5°C (about 9°F). More preferably, the temperature increase is from about 7°C or about 13°F and no more than about 22°C or about 40°F. Gel-type embodiments of the compositions of this invention preferably effect a temperature increase from at least about 13°F upward, preferably up to about 31°F. Jelly-type embodiments of the compositions of this invention preferably effect a temperature increase from at least about 7°F and may effect a temperature increase up to about 27°F. However, this range may vary depending upon the composition.

The compositions of this invention are unexpectedly self-preserving and may not require a preservative. However, a preservative may be added to impart an additional guarantee against microbial growth. A preservative may be selected from preservatives known to those of skill in the art, including, but not limited to, one or more of the following: methylparaben, benzoic acid, sorbic acid, gallic acid, propylparaben or the like. The preservative may be present in the compositions of this invention in an amount from about 0.01% to about 0.75% by weight of the composition. The compositions of this invention may also preferably contain an ester. More preferably, the ester is a fatty acid ester. Most preferably, the ester may include, but is not limited to: isopropyl stearate, isopropyl myristate, isopropyl palmitate, isopropyl laurate and the like. Most preferably, the ester is isopropyl myristate. The compositions of this invention may contain one or more water-soluble cellulose-derived polymers, gums, chitosans or the like. Such polymers contribute to the viscosity and bioadhesiveness of the compositions of this invention. Preferably, such cellulose-derived polymers are hydroxyalkylcellulose polymers. More preferably, the hydroxyalkylcellulose polymer is hydroxypropylcellulose or Klucel®, available commercially from Hercules Incorporated, Wilmington, Delaware. The polyhydric alcohols used in the compositions of this invention are theorized to be useful as warming and heat-generating

agents. Honey functions as an insulating agent, protecting the compositions from becoming too cold. The ester, preferably a fatty acid ester, functions as an emollient and lubricant. The cellulose polymer is useful as a viscosity building agent. The compositions of this invention are unique in that they lubricate, warm and soothe the tissues of the user, especially the oral and vaginal mucous membranes, without conveying a feeling of cold. Moreover, they are smooth and lubricating.

The compositions of this invention may be a liquid, a semi-solid, or a solid depending upon the particular intended use thereof. The compositions of this invention may be formulated as syrupy liquid-gels, pourable gel or thick jellies. Preferably, their viscosities should range from about 1,000 cps to about 7,000 cps for the gels and from about 60,000 cps to about 500,000 cps for the jellies. The compositions of this invention may also be formulated into soft or hard gelatin capsules, suppositories and impregnated into fabrics or polymers.

The compositions of this invention may be used as personal lubricants which convey a feeling of warmth. The feeling of warmth generated by the compositions of this invention is soothing to the skin or mucous membranes where they are applied. The compositions of the invention also possess a sweet and pleasant taste, which is of particular benefit when these compositions are used orally.

The compositions of this invention may also be used as personal moisturizers, which convey a feeling of warmth when applied to vaginal or oral mucosa. Such a warming effect has been found to enhance intimacy and increase pleasure during intimate activities. Flavors and fragrances that enhance different senses and promote relaxation or intimacy may also be added to the compositions of this invention to enhance their effect, both in improving intimacy and in creating a feeling of relaxation.

They may be used as moisturizers which convey a feeling of warmth and relieve vaginal dryness or dry mouth. They may also be

utilized to moisturize skin, and to provide an ameliorating effect for frostbite on extremities over-exposed to the cold. They may be useful for treating conditions of infection on the skin or mucosa while soothing the area of infection.

The compositions of this invention may also be used as a vehicle to deliver medication or other treatment agents to biomembranes including, but not limited to, hormones, antimicrobials, antibacterials, antibiotics, non-steroidal anti-inflammatory agents, spermicides, immunodilators, anaesthetics, plant extracts, vitamins, corticosteroids or antifungal agents and the like.

Antifungal agents are preferably azoles or imidazoles, including but not limited to, miconazole, econazole, terconazole, saperconazole, itraconazole, butaconazole, clotrimazole, tioconazole, fluconazole and ketoconazole, vericonazole, fenticonazole, sertaconazole, posaconazole, bifonazole, oxiconazole, sulconazole, elubiol, vorconazole, isoconazole, flutrimazole, tioconazole and their pharmaceutically acceptable salts and the like. Other antifungal agents may include an allylamine or one from other chemical families, including but not limited to, ternafine, naftifine, amorolfine, butenafine, ciclopirox, griseofulvin, undecyclenic acid, haloprogin, tolnaftate, nystatin, iodine, rilopirox, BAY 108888, purpuromycin and their pharmaceutically acceptable salts. Particularly suited for use in the compositions of this invention are insoluble or sparingly-soluble azole compounds that are capable of exhibiting both antifungal and antibacterial activity upon administration in conjunction with the methods of this invention.

Another embodiment of the invention are compositions for vulvovaginal or other mucosal use containing one or more antibiotics. The antibiotic may be chosen from the group including, but not limited to, metronidazole, clindamycin, tinidazole, ornidazole, secnidazole, refaximin, trospectomycin, purpuromycin and

their pharmaceutically acceptable salts and the like.

Another embodiment of the compositions of this invention include compositions for vulvovaginal or other mucosal use containing one or more antiviral agents. Antiviral agents may preferably include, but are not limited to, immunomodulators, more preferably imiquimod, its derivatives, podofilox, podophyllin, interferon alpha, reticolos, cidofovir, nonoxynol-9 and their pharmaceutically acceptable salts and the like.

Still other embodiments of the compositions of this invention are compositions that include one or more spermicides. The spermicides may preferably include, but are not limited to, nonoxynol-9, octoxynol-9, dodecaethyleneglycol monolaurate, Laureth 10S, and Methoxypolyoxyethyleneglycol 550 Laurate and the like.

Still other embodiments of the compositions of this invention are compositions containing antimicrobial agents. The antimicrobial agents may preferably include, but are not limited to, chlorohexidine gluconate, sodium polystyrene sulfonate, sodium cellulose sulfate, silver particles of micro- and sub-micrometer sizes, silver salts and other antibacterial agents known to the art.

Yet other embodiments of the compositions of this invention are compositions that may include local anesthetics. The local anesthetics may preferably include, but are not limited to, benzocaine, lidocaine, dibucaine, benzyl alcohol, camphor, resorcinol, menthol and diphenylhydramine hydrochloride and the like.

Compositions of the invention may also include plant extracts such as aloe, witch hazel, chamomile, hydrogenated soy oil and colloidal oatmeal, vitamins such as vitamin A, D or E and corticosteroids such as hydrocortisone acetate.

Another embodiment of the compositions and methods of this invention include compositions for vulvovaginal use containing one or more hormones for treating a decrease in estrogen secretion in the woman in need of estrogen replacement such as women with vaginal

atrophy. The hormones may preferably include, but are not limited to, estrogen selected from the group consisting of estradiol, estradiol benzoate, estradiol cypionate, estradiol dipropionate, estradiol enanthate, conjugated estrogen, estriol, estrone, estrone sulfate, ethinyl estradiol, estrofurate, quinestrol and mestranol.

In another embodiment of the compositions and methods of this invention, the compositions may be useful for treating female sexual dysfunction by themselves as they may serve to increase blood flow to areas on which they are applied by increasing temperature thereon. Alternatively, they may contain agents known to those of skill in the art to treat female sexual dysfunction (including different aspects of female sexual dysfunction such as female sexual arousal disorder, hypoactive sexual desire disorder, orgasmic disorder and the like) as well as those that treat dyspareunia and/or vaginismus, or vulvodynia and to relieve pain upon intercourse. Such agents include hormones such as estrogen, prostaglandin, testosterone; calcium channel blockers, cholinergic modulators, alpha-adrenergic receptor antagonist, beta-adrenergic receptor agonists, camp-dependent protein kinase activators, superoxide scavengers, potassium channel activators, estrogen-like compounds, testosterone-like compounds, benzodiazepines, adrenergic nerve inhibitors, HMG-CoA reductase inhibitors, smooth muscle relaxants, adenosine receptor modulators and adenylyl cyclase activators. Such agents include phosphodiesterase-5 inhibitors and the like. The compositions of the invention may also contain vasodilators such as methyl nicotinate, histamine hydrochloride and very small non-irritating amounts of methyl salicylate.

Another embodiment of the compositions and methods of this invention include compositions for vulvovaginal use containing one or more analgesics and/or nonsteroidal anti-inflammatory agents for treating dysmenorrhea or menstrual cramping. The analgesics and nonsteroidal anti-inflammatory agents may preferably include, but are not limited to, aspirin, ibuprofen, indomethacin,

phenylbutazone, bromfenac, fenamate, sulindac, nabumetone, ketorolac, and naproxen and the like.

Yet another embodiment of the compositions and methods of this invention include compositions for oral and vulvovaginal or other mucosal use relates to a method of enhancing the absorption of active agents from the applied compositions into the mucosal membrane by increasing the composition and mucosal tissue temperature via interaction of the polyhydric alcohols in the compositions and moisture on the mucosa and subsequently released heat.

Yet another embodiment of the compositions of this invention include compositions for vulvovaginal use relates to compositions and methods for preventing and/or treating dysmenorrhea by intravaginal warming or heating. Preferably, the composition heats the intravaginal area to a temperature preferably between about 37°C and about 42°C, more preferably between about 38°C and about 41°C. The compositions of invention for use in such a method may optionally contain active agents such as analgesics and nonsteroidal anti-inflammatory agents for dysmenorrhea treatment. The composition of the invention may be administered directly into the vagina by an applicator, or be impregnated into vaginal devices such as tampon for intravaginal applications.

The compositions of this invention may be manufactured as a coating of a tampon, or dispersing throughout the absorbent tampon material, or enclosed inside as a core of a tampon. The compositions of this invention for the warming tampon for preventing and/or treating dysmenorrhea preferably include a mixture of polyethylene glycols of various molecular weights produced by The Dow Chemical Company (Midland, MI) under the trade names of CARBOWAX SENTRY PEG 300 NF, CARBOWAX SENTRY PEG 400 NF, CARBOWAX SENTRY PEG 600 NF, CARBOWAX SENTRY PEG 900 NF, CARBOWAX SENTRY PEG 1000 NF, CARBOWAX SENTRY PEG 1450 NF, CARBOWAX SENTRY PEG 3500 NF, CARBOWAX SENTRY PEG 4000 NF, CARBOWAX SENTRY PEG 4600 NF, and CARBOWAX SENTRY

PEG 8000 NF. The compositions of this invention for dysmenorrhea prophylaxis and treatment may contain one or more water-soluble cellulose-derived polymers and gums that form gels around the polyhydric alcohols such as glycerin, propylene glycol and polyethylene glycols thus reducing the dissolution of the polyhydric alcohols, prolonging the solvation heat release, and regulating the elevated temperature in the preferred temperature range.

The compositions of this invention may be applied to the oral or vaginal mucosal tissues manually or via a swab or vaginal applicator or in any way known to those of ordinary skill in the art.

This invention also relates to a method of determining and comparing relative amounts of irritation caused by particular sources using the EpiDerm™ Skin Model Assay as described in Example 1, such as compositions applied to skin or mucosal cells. The following Example 1 exemplifies the use of the method of this invention.

Example 1: EpiDerm™ Skin Model Assay to Test Irritation of Lubricants

The method designated as EpiDerm™ Skin Model assay uses the epithelial cells derived from human skin as target cells and is commercially available from the MatTek Corporation. . This assay is described in Berridge, M.V., et al. (1996) *The Biochemical and Cellular Basis of Cell Proliferation Assays That Use Tetrazolium Salts*. **Biochemica 4**: 14-19. The test materials are applied directly to the epithelial cell culture surface. This test has not previously been used for determining toxicity of test materials. The toxicity of the test material is evaluated on the basis of relative tissue viability vs time. The actual Tissue Viability is determined by NAD(P)H-dependent microsomal enzyme reduction of MTT in control and test article treated cultures. The negative control used in this assay was deionized water and the positive control was Triton X-100. The exposed cell cultures were incubated for 4, 8, 16 and 24 hours

and assayed for reduction of MTT. The data is presented below in Figures 1 through 4 in the form of Relative Survival (relative MTT reduction) versus Exposure Time. Relative irritation in this assay is expressed by the percent survival rate of epiderm cells over a period of 24 hours. Products with higher relative survival rates are less toxic or less irritating. The survival rate of four compositions of this invention ranged between 81.3% and 90.3%, indicating that the compositions of this invention are essentially non-irritating. The survival rate of four compositions of this invention ranged between about 81.3% and about 90.3%, indicating that the compositions of this invention are essentially non-irritating. Thus, preferably, at least about 50%, more preferably, at least about 80% and most preferably, at least about 90% of cells survive in this test when exposed to the compositions of this invention as measured by the Epiderm Skin Model Bioassay.

Figures 1 through 4 summarize the results of Epiderm Skin Model Bioassay. The data is plotted as % Viable Cells vs the Exposure Time ranging from 4 to 24 hours. Figures 1 and 2 represent the results for two compositions of this invention, Composition 1 and Composition 2 respectively. Figure 3 represents the results of K-Y® Liquid, an established personal lubricant on the market. K-Y® Liquid is established as safe and nonirritating in animal and human testing and long-term human use history. Results for K-Y® Liquid showed 100.3% viable cells after 24 hour of exposure (Figure 3).

Example 1 of the invention (Figure 1) and Example 2 of the invention (Figure 2) showed 91.1% and 96.9% viable cells respectively. Figure 4 shows the results of a warming composition known to the trade. This product uses plant materials like cinnamon, clove, ginger cloves and orange and others for a warming sensation. The results show only 37.6% viable cells after 24 hours of exposure to this product. This indicates that such compositions will be irritating to the skin and mucous membranes. Compositions 1 and 2 of

this invention, with 91.1% and 96.9% viable cells respectively, will be practically nonirritating. Positive control (Triton X-100) has only 22.4% viable cells at the 8-hour interval.

Example 2: Generation Of Warmth

The compositions of this invention are anhydrous and contain one or more polyhydric alcohol. When combined with water, the polyhydric alcohols used in the compositions of this invention generate an increase in temperature that has a soothing effect on the tissues these compositions are applied. In actual use the compositions of the invention interact with the moisture of the vaginal or oral mucosa, thereby increasing the temperature or generating feeling of warmth.

The "Generation of warmth" data summarized in Table 1 below, was generated by mixing 20 ml of each of the ingredients in Composition 1 and Composition 1 of this invention with 20 ml of water. The temperature of the product and that of water were recorded before water was added to the product. After the addition of water the mixture was mixed for two minutes and the actual temperature was recorded. Glycerin, Propylene Glycol and Honey are the ingredients in Composition 1. It is clear from Table 1. that when mixed with water the temperature of the mixture rises by 9.0° F for Glycerin, 13.5° F for Propylene Glycol, 17.0° F for Polyethylene Glycol 400 and 12.5° F for composition Example1 of this invention. The calculated rise in temperature for Composition 1, based on the rise in temperature and the % w/w quantity of each individual ingredient in the composition was 10.875° F. The actual recorded temperature rise for Composition 1. was 12.5° F which is 1.625° F higher than expected which indicates that there is an unexpected increase in temperature resulting from the combination of ingredients.

GENERATION OF WARMTH (RISE IN TEMPERATURE °F) DATA BY MIXING EQUAL QUANTITYOF EACH PRODUCT WITH WATER

Product Name	Temperature of the Product (°F)	Temperature of Water (°F)	Average Expected Temperature (°F)	Actual Temperature (°F)	Rise in Temperature (°F) (Expected Minus Actual)
Glycerin Assay	69.0	71.0	71.0	79.0	9.0
Propylene Glycol Assay	72.4	71.0	71.7	85.2	13.5
Honey	74.0	71.0	72.5	74.0	1.5
K – Y Warming®	74.0	71.0	72.5	85.0	12.5
Isopropyl Myristate	75.0	74.1	74.5	75.2	0.7
Polysorbate 60	75.0	74.1	72.5	83.1	10.6
Polyethylene Glycol 400	72.0	71.0	71.5	88.5	17.0

Calculated Rise in Temperature: In order to determine the expected rise in temperature from each composition, the percentage of each component in such composition was multiplied by the temperature increase generated by such component alone to obtain its expected contribution to the temperature increase. These values were added together to calculate the total expected temperature rise. These values were then compared with the actual temperature rise generated by each composition. For example, the calculated rise in temperature generated by the "K-Y Warming®" composition in the table above was found as follows and compared with the actual temperature rise to determine the unexpectedly higher generation of warmth of

the composition:

Propylene Glycol (50% of 13.5)	= 6.75
Glycerin (45% 0f 9.0)	= 4.05
Honey (5% of 1.5)	= 0.075
Total	10.875

Difference: 12.5 - 10.875 = 1.625

Example 3: Effect of Water Content on Generation of Warmth

On contact with moisture or water the heat of solution is responsible for the warming action of the compositions of this invention. There is a concern that accidental contamination with water or prolonged exposure to excessive moisture, the warming capacity of the product may be adversely effected. According to this example, water was added to compositions of this invention varying from about 1% to about 10% as outlined in Table 2 below. The contents were thoroughly mixed and the samples were allowed to stay at room temperature for 24 hour following which the generation of warmth was determined as outlined in the following paragraph. The results show that rise in temperature is proportionately decreased depending on the quantity of water added but there is still an 8.5°F increase in temperature at about 10% water addition.

The results of this example are set forth in Table 2 below.

Table 2: Effect Of Water Content On Generation Of Warmth For K-Y Warming®.

Product Name	Temperature of the Sample (°F)	Temperature of Water (°F)	Average Expected Temperature (°F)	Actual Temperature (°F)	Rise in Temperature (°F) (Expected Minus Actual)
No Water	73.80	70.00	71.90	83.50	11.60
1% Water	73.90	70.00	71.95	82.20	10.25
2% Water	72.30	70.00	71.95	81.70	9.85
3% Water	72.30	70.00	71.15	80.40	9.25
4% water	72.20	70.00	71.15	80.70	9.60
5% Water	71.60	70.00	70.80	80.40	9.60
6% Water	71.60	70.00	70.80	80.40	9.60
7% Water	71.50	70.00	70.75	80.20	9.45
8% Water	71.60	70.00	70.80	80.20	9.40
9% Water	70.90	70.00	70.45	79.50	9.05
10% Water	70.50	70.00	70.25	79.00	8.50

Example 4: Perception Of Warmth In Human Use

A Human Use Study was conducted with 246 subjects. The data generated by this study are summarized below in Table 2. The subjects were asked to use compositions of this invention. They were asked three questions regarding the perception of warmth while using the product, as follows:

1. Does it warm on contact?
2. Does it feel warm?
3. Does it not feel cold?

The subjects were asked to register their response as Excellent, Very Good, Good, Fair and Poor. The positive responses are summarized in Table 2.

Table 3: PERCEPTION OF WARMTH IN HUMAN USE STUDY WITH 246 HUMAN SUBJECTS USING COMPOSITION EXAMPLE 1 OF THE INVENTION

QUESTION ASKED	POSITIVE RESPONSE (%)
Warms on Contact	
Excellent	25.12
Very Good	31.88
Good	24.64
Total	81.64
Feels Warm	
Excellent	30.88
Very Good	28.92
Good	25.98
Total	85.78
Does Not Feel Cold	
Excellent	54.37
Very Good	29.61
Good	10.19
Total	94.53

As set forth in Table 3 above, 81.64% of the subjects registered a positive response that the product "warms on contact", 85.78% subjects felt that the product "feels warm" while 94.53% subjects registered that the product "does not feel cold".

Example 5: Comparison Of Lubricity

Ahmad et al. in U.S. Patent No. 6,139,848, which is hereby incorporated herein by reference, describe a method to test lubricity of various personal lubricants known to the trade. In the described test method, the lubricity of various marketed personal lubricants was determined over a period of 300 seconds (5 minutes). The lubricity data disclosed in this patent indicates that K-Y Liquid® lubricant had a higher lubricity and was longer lasting during the 300 seconds test period than the competitive products. The lubricity data set forth in U.S. Patent No. 6,139,848 has a negative (-) sign during the "push" and positive (+) sign during the "pull" phase of the experiment. Compositions of this invention were tested using the lubricity test set forth in U.S. Patent No.

6,129,848. However, the test duration was successfully extended to 16 minutes (960 seconds) and the data was treated to "curve-fit" to eliminate the negative (-) sign. The lubricity data for the composition 1 of this invention is compared with the data for K-Y Liquid® in Figure 5. The data indicate that Composition 1 of this invention has a higher lubricity as compare to K-Y Liquid® and that Composition 1 maintains the high lubricity for an extended period of 16 minutes (960 minutes) and is therefore longer lasting.

Example 6: Heat of Solution

The warming effect of the compositions of this invention is believed to be caused by generating heat of solution, as opposed to creating the conditions for exothermic reactions. Exothermic reactions result in evolution of heat due to a chemical reaction between two chemicals and are uncontrolled. Such an exothermic chemical reaction may generate new products or chemical entities, some of which may not be suitable for human tissues. In contrast, when a solution is formed there is an energy change because of the difference between the forces of attraction of unlike and like molecules. Specifically, bonds are broken between molecules of the each component being mixed and new bonds are formed between neighboring molecules of the product mixture or solution. This mechanism is different from a Heat of Reaction because there is no chemical rearrangement of the constituent atoms to form products from reactants. As can be seen from the following experiment, maximum heat generated or the maximum rise in temperature is no more than 18.8 °F, which makes these compositions very mild and safe.

The solution process for the compositions of this invention (COMPOSITION A) in, for example, vaginal fluids ("X H_2O") can be represented by the following physical equation:

COMPOSITION A (l) + X H_2O (l) → COMPOSITION A (X H_2O)

The designation "COMPOSITION 15 (X H_2O)" represents that the product is a solution of 1 (mol) of COMPOSITION 15 in X (mol) of H_2O. Thus, using COMPOSITION 15, a composition according to this invention, as a personal lubricant does not change the existing amount of naturally occurring vaginal fluids. It simply forms a solution with them.

The maximum temperature increase possible from the generation of heat by use of the compositions of this invention may be measured using thermodynamic principles. For example, Differential Scanning Calorimetry (DSC) was employed to characterize the heat released (or, "Energy Release Index") by the compositions of this invention when they come into contact with water to form a solution. In this testing, the energy released when a thin film of a particular composition was applied to a thin film of water was measured. The results of a typical test are presented in Figure 6. The area of the exothermic (i.e., negative) peak represents the total energy released during the formation of a solution of the composition of this invention and water. Table 1 summarizes the energy released for this series of experiments.

Table 1: Summary of DSC Measurements of Heat Released By COMPOSITION 15 / Water

Experiment #	Composition of the Invention (mg)	Energy Released (mJ)
1	17.85	398.878
2	22.5	355.108
3	28.32	267.229
Average	22.89	340.405
Standard Deviation	5.25	67.045

The energy release measured by the DSC is representative of the maximum energy which would be seen on the surface of the vaginal tissue. This is because the heat flux (energy flow) into the thin

film of water during the formation of the solution measured by the DSC is equivalent to the heat flux (energy flow) which would be in the fluid on the surface of the vaginal tissue. Therefore, thermodynamics can be used to calculate the maximum possible temperature rise as follows:

$$Q_{max} = C_{pm}\ \Delta T_{max} \qquad \textbf{(Equation 1)}$$

where, Q_{max} represents the Maximum Energy Released (or, "Maximum Energy Release Index") during contact (formation of solution) of Composition 15 and water; C_{pm} represents Heat Capacity of Solution of Composition 15 and Water; and ΔT_{max} represents Maximum Temperature Rise. Thus, rearranging Equation 1, we can calculate ΔT_{max}, the Maximum Temperature Rise, based upon the known or measured values of the Maximum Energy Released and the Heat Capacity of Solution of Composition 15, as follows:

$$\Delta T_{max} = Q_{max} / C_{pm} \qquad \textbf{(Equation 2)}$$

By assuming a normal distribution, the experimental results in Table 1 can be used to arrive at a worst case estimate for the maximum value of Q_{max} as follows:

Q_{max} = **{Average Experimental Energy Release + 3 x (Standard Deviation of Experimental Energy Release)} / (Average Quantity of Composition 15)**

= **{(340.405 mJ) + (3) (67.045 mJ)} / (22.89 mg)**

= **(541.539 mJ / 22.89mg)**

(Equation 3)

(Using this as the upper limit represents the 99.73% upper confidence limit for the normal distribution.)

In the case of C_{pm}, the smaller of the C_p for Composition 15 and the C_p for Water can be used to arrive at a worst case estimate for its minimum value. Since,

C_p (Composition 15) = 0.54 cal / (g - °C)

C_p (Composition 15) = 1.00 cal / (g - °C)

then,

C_{pm} (worst case minimum) = 0.54 cal / (g - °C) (Equation 4)

Therefore, a worst case estimate of the maximum temperature increase possible from the generation of heat by for Composition 15 can be arrived at by using the combining Equations 2, 3, and 4 as follows:

$\Delta T_{max} = Q_{max} / C_{pm}$
= ((541.539 mJ)/(22.89 mg))/(0.54 cal / (g - °C) x 0.23901 cal / J

= 10.5 °C or = 18.8 °F

Thus, the maximum heat released upon use of Composition 15 is, at the most, about 10.5°C or 18.8 °F, a relatively small increase in heat, indicating that the temperature increase effected by the compositions of this invention are safe and comfortable to the user.

Example 7: Generation of Warmth

Compositions 10, 11 and 12 were tested in accordance with the following procedure to determine the extent to which said compositions generate warmth upon mixture with water. Data was generated by mixing 20 ml of each composition with 20 ml of water. The temperature of the composition and that of water were recorded before water was added to the composition After the addition of water the contents were mixed for two minutes and the actual temperature was recorded. The results are set forth in the following Table:

GENERATION OF WARMTH (RISE IN TEMPERATURE °F) DATA BY MIXING EQUAL QUANTITY OF EACH COMPOSITION WITH WATER.

Product Name	Temperature of the Product (°F)	Temperature of Water (°F)	Average Expected Temperature (°F)	Actual Temperature (°F)	Rise in Temperature (°F) (Expected Minus Actual)
Rise In Temperature For Compositions For Compositions Of The Invention					
Composition 10	73.00	70.3	71.6	87.3	15.7
Composition 11	73.00	70.3	71.6	83.2	11.6
Composition 1●	73.00	70.3	71.6	87.1	15.5
Rise In Temperature For The Individual Components Of The Compositions					
Polyethylene Glycol 400	72.0	71.0	71.5	88.5	17.0
Propylene Glycol	72.4	71.0	71.7	85.2	13.5
Glycerin	69.0	71.0	70.0	79.0	9.0

We calculated the rise in temperature For Compositions 10, 11 and 12:

Composition 10

Propylene Glycol (38 % of 13.5) = 5.13

Polyethylene Glycol 400 (61.5% 0f 17.0) = 10.45

Total: 15.58 °F

Composition 11

For Composition 11 the calculated Rise in Temperature is 15.58 °F

Composition 12

For Composition 12 the calculated Rise in Temperature is 15.15 °F

Calculated temperature for all three compositions is very close to the Actual Rise in Temperature.

Example 8: Comparison of Lubricity

Using the method to test and compare lubricity of various personal lubricants set forth in Example 3 above, the lubricity of the compositions of this invention was determined. The following is the summary of the results:

The Gel compositions of this invention are as lubricating as the aqueous gel compositions described in the US Patent No. 6,139,848 by Ahmad et al. In Figure 7, the lubricity of commercially available KY® Jelly was measured both in its commercially-available form and in a 1:1 dilution with water. Upon dilution, the lubricity did not increase substantially.

The Jelly compositions of this invention are more lubricating as compared to the state of the art aqueous jellies known to the trade. Composition 14 of this invention was measured with respect to lubricity as initially made and in a 1:1 dilution with water. Surprisingly, its lubricity increases substantially (about four-fold) upon dilution. These data are represented in Figure 8. Thus, the jelly compositions of this invention become more lubricious or their lubricity is increased when these compositions are diluted with water in a 1:1 ratio. Figure 9 demonstrates a comparison of the lubricities of KY® Jelly and Composition 14 in their initial forms. Figure 10 illustrates the lubricities of two warming gel compositions of this invention, Compositions 13 and 14, showing their high lubricities. Figure 11 shows KY* Ultragel and diluted Composition 14.

Example 9: Compositions Of The Invention

The following compositions of this invention were made as follows: first, propylene glycol and glycerin were mixed. A preservative and the insulating agent were then added to the mixture in the same container. The mixture was then heated to from about 35° C to about 45 ° C to completely dissolve the preservative. The

mixture was then cooled. The gel and jelly compositions were made by mixing propylene glycol, polyethylene glycol and hydroxypropylcellulose in a high-speed mixer at a temperature of between about 60° C to about 70 ° C until a smooth gel or jelly was obtained. The resulting gel or jelly was cooled to a temperature of between about 45° C and about 55 ° C and lactic acid was added. The mass was continuously mixed for about 15 minutes or until the lactic acid was dissolved. The mass was then cooled to room temperature.

Composition 1:

Propylene Glycol	50.00%
Glycerin	45.00%
Honey	5.00%

Composition 2:

Propylene Glycol	50.00%
Glycerin	20.00%
Isopropyl Myristate	27.00%
Polysorbate 60	3.00%

Composition 3:

Propylene Glycol	95.00%
Honey	5.00%

Composition 4:

Propylene Glycol	50.00%
Glycerin	20.00%
Isopropyl Myristate	29.50%
Klucel HF	0.50%

Composition 5:

Propylene Glycol	99.50%
Klucel HF	0.50%

Composition 6:

Propylene Glycol	49.80%
Glycerin	45.00%
Honey	5.00%
Preservative	0.20%

Composition 7:

Miconazole Nitrate	2.00%
Propylene Glycol	49.80%
Glycerin	43.00%
Honey	5.00%
Preservative	0.20%

Composition 8:

Fluconazole	2.00%
Propylene Glycol	49.80%
Glycerin	43.00%
Honey	5.00%
Preservative	0.20%

Composition 9:

Metronidazole	3.00%
Propylene Glycol	49.80%
Glycerin	42.00%
Honey	5.00%
Preservative	0.20%

Composition 10 (Gel):

Propylene Glycol	38.00
Polyethylene Glycol 400	61.05
Lactic Acid	00.20

Hydroxypropylcellulose	0.75
Composition 11 (Jelly):	
Propylene Glycol	37.00
Polyethylene Glycol 400	61.05
Lactic Acid	00.20
Hydroxypropylcellulose	1.75
Composition 12 (Gel):	
Propylene Glycol	48.00
Polyethylene Glycol 400	51.30
Lactic Acid	0.20
Hydroxypropylcellulose	0.50
Composition 13 (Jelly):	
Propylene Glycol	48.55
Polyethylene Glycol 400	50.00
Lactic Acid	0.20
Hydroxypropylcellulose	1.25
Composition 14 (Jelly:	
Propylene Glycol	98.55
Lactic Acid	0.20
Hydroxypropylcellulose	1.25
Composition 15 (Jelly):	
Polyethylene Glycol 400	98.55
Lactic Acid	0.20
Hydroxypropylcellulose	1.25
Composition 16 (Gel):	
Polyethylene Glycol 400	99.50
Lactic Acid	0.20
Hydroxypropylcellulose	0.30

Composition 17 (Gel):	
Propylene Glycol	74.50
Glycerin	25.00
Lactic Acid	0.20
Hydroxypropylcellulose	0.30
Composition 18 (Gel):	
Propylene Glycol	74.50
Polyethylene Glycol 400	25.00
Lactic Acid	0.20
Hydroxypropylcellulose	0.30
Composition 19 (Gel):	
Propylene Glycol	69.50
Polyethylene Glycol 400	15.00
Glycerin	15.00
Lactic Acid	2.00
Hydroxypropylcellulose	0.30
Composition 20 (Jelly):	
Propylene Glycol	73.55
Polyethylene Glycol 400	25.00
Lactic Acid	0.20
Hydroxypropylcellulose	1.25
Composition 21:	
Propylene Glycol	47.80
Polyethylene Glycol 400	48.00
Hydroxypropylcellulose (Klucel HF)	2.00
Lactic acid	0.20
Miconazole Nitrate	2.00

Composition 22:

Propylene Glycol	35.00
Polyethylene Glycol 400	60.80
Hydroxypropylcellulose (Klucel HF)	2.00
Lactic acid	0.20
Miconazole Nitrate	2.00

Composition 23:

Propylene Glycol	48.80
Polyethylene Glycol 400	48.00
Hydroxypropylcellulose (Klucel HF)	2.00
Miconazole Nitrate	2.00

Composition 24:

Propylene Glycol	47.80
Polyethylene Glycol 400	46.00
Hydroxypropylcellulose (Klucel HF)	1.00
Polyvinylpyrilidone (K29-32)	3.00
Lactic acid	0.20
Miconazole Nitrate	2.00

Composition 25:

Propylene Glycol	48.80
Polyethylene Glycol 400	48.00
Hydroxypropylcellulose (Klucel HF)	2.00
Itraconazole	2.00

Example 10: *In Vitro* Testing for Antibacterial and Antifungal Activity

In Vitro Time-Kill Studies were used to test the antibacterial and antifungal activity of the compositions of this invention. A battery of vaginal anaerobes known to cause bacterial vaginal

infections (BV), *Candida albicans* which is responsible for vulvovaginal candidiasis (VVC) and strains of *lactobacilli* were used to determine the length of contact time required to inhibit and kill these test organisms. The results of this test are summarized in Table 3. The results show that Compositions 1, 2 and 3 of the invention kill the BV causing bacteria and *Candida albicans* in 0 hour or almost instantaneously.

Surprisingly the compositions of the invention did not have any adverse effect on lactobacilli that continued to grow even after 24 hours. These results show that the compositions of this invention will be effective to treat both the fungal and bacterial vaginal infections and are selective enough not to harm lactobacilli.

Table 3

Results of *In Vitro* Evaluation: Activities of Compositions of the Invention

	EXAMPLE				
Organism	**Composition 21**	**Composition 22**	**Monistat 3 Vaginal Cream**	**Composition 23**	**MetroGel-Vaginal**
Gardnerella vaginalis	0	0	0	0	2
Gardnerella vaginalis	0	0	0	0	4
Gardnerella vaginalis	0	0	0	0	>9<23
Gardnerella vaginalis	0	0	2	1	>9<23
Peptostreptococcus magnus	4	3	6	7	0
Peptostreptococcus magnus	4	8	5	>7<23	0
Peptostreptococcus magnus	1	3	4	1	0
Peptostreptococcus tetradius	0	0	1	1	0
Peptostreptococcus tetradius	0	0	1	1	0
Peptostreptococcus tetradius	0	0	2	1	0
Peptostreptococcus asaccharolyticus	0	0	2	1	0
Peptostreptococcus asaccharolyticus	0	0	2	0	0
Peptostreptococcus asaccharolyticus	0	0	1	2	0
Prevotella bivia	0	0	1	1	0
Prevotella bivia	0	0	1	1	0
Prevotella bivia	0	0	1	1	0
Prevotella disiens	0	0	1	0	0
Prevotella disiens	0	0	1	0	0
Prevotella disiens	0	0	1	0	0

Prevotella intermedia	0	0	1	0	0
Prevotella intermedia	0	0	1	0	0
Prevotella melaninogenica	0	0	1	0	0
Prevotella melaninogenica	0	0	1	0	0
Mobiluncus mulieris	0	0	>24	0	1
Mobiluncus mulieris	0	0		0	3
Lactobacillus plantarum	0	0		1	0
Lactobacillus species	4	8		3	>8<23
Lactobacillus acidophilus	>24	>24		>24	>24
Lactobacillus acidophilus	>24	>24		>24	24
Candida albicans	0	0		0	>8<23
B.fragilis	1	0		1	0
B.theta	0	1		0	0

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